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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,169	10/21/2003	R. Kent Hermsmeyer	HME/7961.0013	3934

29085 7590 09/25/2009

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
09/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,169	HERMSMEYER, R. KENT	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☒ Claim(s) *4-10* is/are allowed.

6)☒ Claim(s) *1-3 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The office acknowledges the receipt of Applicants' remarks/arguments in response to the office action. Claims 1-23 are pending, claims 17-23 are withdrawn. Claims 1-16 are examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 1-16 under 35 U.S.C. 112, first paragraph, enablement rejection has been fully considered and not found to be persuasive. Accordingly, the rejection is maintained and is given below for Applicants' convenience. Applicants' arguments and submission of scientific data "Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor β," Endocrinology, 139(I0):4252-4263 (1998) regarding the 103(a) rejections have been found to be persuasive and hence 103(a) rejections have been withdrawn. The 112(1) rejection from previous office action is maintained and accordingly, the rejection is made Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for estriol (examples 3 and 4) in a method of treating vasospasm and effect of estriol on diameter of coronary arteries does not reasonably provide enablement of reducing the vascular hyperreactivity in vascular

muscle cells comprising exposing the vascular muscle cells with all other estrogen receptor agonist (ER) that has a higher relative selectivity than does genistein for ER-beta compared to ER-alpha and further administering the same to a patient in concert with a hormone replacement therapy. The specification does not teach administration of any other ER-beta ligand other than estriol in reducing vascular hyperreactivity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the Invention:

The rejected claims (1-16) are drawn to a method of reducing vascular hyperreactivity in vascular muscle cells comprising administering to the patient an effective amount of a selective estrogen beta receptor agonist that has a higher relative selectivity than that of genistein for estrogen receptor beta compared to estrogen

receptor alpha and administration of the same in concert with a hormone replacement therapy (claims 11-12).

(2) Breadth of the claims:

The clams are broad with respect to the number of estrogen beta receptor agonist compounds as they are drawn to a method of reducing the vascular hyperreactivity in vascular smooth muscle cells. As indicated in the specification vascular hyperreactivity is manifested by different conditions that include coronary arterial vasospasm, hyperactivity of peripheral arteries etc. (claims 2-3). Claims 11 and 12 are directed to reducing the vascular hyperreactivity administering the ER-beta agonist in concert with hormone replacement therapy. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

(3) Guidance of the Specification and (4) Working Examples:

The guidance given by the specification to a method of reducing vascular hyperreactivity in vascular smooth muscle cells is 1) comparison of effects of estriol with 3βAdiol and epiestriol in vitro on Ca2+ responses in rhesus coronary VMC (example 9) 2) estriol in a method of treating vasospasm and effect of estriol on diameter of coronary arteries (examples 3 and 4) and comparison of different estrogen beta receptor agonists (genistein, DPN) 3) in measurement of estrogen receptor beta activity.

The specification provides example for comparison of effects of estriol with 3βAdiol and epiestriol in vitro on Ca2+ responses in rhesus coronary VMC, to a method of treating vasospasm by administration of the drug epiestriol and its effect on diameter of coronary arteries.

(8) State of the art:

The prior art teaches genistein and estradiol in a method of treating vasospasm and reducing the incidence or severity of vascular hyperreactivity in a patient. The prior art Meyers, J. Med. Chem, 44,:4230-4251 (2001) teaches the relative affinity of few agonists for ER-alpha and ER-beta. Bhagawat (WO 01/49673) teaches ER modulators, Ohman et al. (U.S 2003/0032779) teaches ER ligands, Barlaam et al. teaches ER-beta ligands (U.S. 6,518,301) and WAY-202196 is a known estrogen beta receptor agonist (see Abstract, Cristofaro et al, Critical Care Medicine, 2006, vol. 34). Lahm et al. (Am J Physiol Regal Integr Comp. Physiol. 295, 1486-93) teaches that selective estrogen receptor alpha and estrogen receptor beta agonists rapidly decrease pulmonary artery vasoconstriction by a nitric oxide mechanism (See Abstract). Harris et al. (Endocrinology, 144, 10, 4241-49) teach an ER-beta selective ligand, ERB-041. The authors state that they expected the compound would be useful in hormone therapy as ER-beta is an attractive drug target for hormone therapy. However, the authors found that the ER-beta selective ligand, ERB-041 is inactive in a large panel of estrogen responsive models and does not prevent bone loss or weight gain after overiectomy (p 4246, col. 2, last para). Also side effects of estriol that has been reported to FDA include contraindication to medical treatment, burning sensation, fungal infections etc (http://www.patientsville.com/medication/estriol_side_effects.htm, Estriol Side Effects Report #5318690-8).

5) The relative skill of those in the art:

The relative skill of those in the medical treatment art is high, requiring advanced education and training.

(6) The predictability of art:

Despite the advanced training of the ordinary practitioners in the pharmaceutical development and medical treatment arts, the arts are highly unpredictable. The state of the art is such that it is not possible to predict the activity of a compound, whether in vitro or in vivo, based on the structure or function alone. Typically, for the development of a method of treating a disease, a certain pharmacological property of a compound, such as receptor binding or activation, or cytotoxicity, must be tested or verified in an in vitro model. The in vitro activity of a series of compounds must typically be verified individually. In order to predict the in vivo activity of a compound based on the in vitro assay, the assay itself must be definitively well correlated to the pathophysiology of a target disease and verified as being predictive of the in vivo activity of a compound. For example, if a receptor is known to be overactivated in the pathophysiology of a disease, the ordinary practitioner would predict that a compound that inhibits the activation of the receptor may be useful for the treatment of said disease. However, even for in vitro models that involve receptors known to be involved in the pathophysiology of a disease, translating the in vitro efficacy of a compound to in vivo efficacy for the treatment of a disease is notoriously unpredictable unless the correlation has been conclusively verified. Further, the in vivo efficacy of a compound is not only determined by the affinity or activity of the compound on its target receptor in a validated in vitro assay, but by a range of other factors including the bioavailability of the compound, its

pharmacokinetic profile, and the specificity of the compound for the desired target versus other potential targets. It must also be accepted that in vitro testing has its limitations, at least in part because isolated tissues can never fully represent the complex integrated biological systems operating in vivo. The claims of the instant invention are broad with respect to estrogen receptor beta agonists that have a higher selectivity than does genistein for ER-beta compared to ER-alpha. According to Harris et al's studies (Endocrinology, 144, 10, 4241-49) not all selective ER-beta agonists have the same properties. In fact the compound, ERB-041 is inactive in a large panel of estrogen responsive models and does not prevent bone loss or weight gain after overiectomy (p 4246, col. 2, last para) and may not be useful in hormone therapy. Accordingly, it is unpredictable that all ER-beta selective agonists would reduce vascular hyperreactivity in vascular smooth muscle cells and be in concert with the hormone replacement therapy. Also it is known in the art that (Lahm et al. Am J Physiol Regal Integr Comp. Physiol. 295, 1486-93), selective estrogen receptor alpha rapidly decrease pulmonary artery vasoconstriction by a nitric oxide mechanism. Estriol has been found to have side effects in humans (see state of the art, above).The claims are broad with respect to ER-beta agonists and there is a high degree of unpredictability involved. Despite the advanced training in the medical treatment arts, the arts are highly unpredictable.

(7) The Quantity of Experimentation Necessary:

In order to practice the above claimed invention, one of ordinary skill in the art would have to first envision formulation, dosage, duration, route and, in the case of

human treatment, an appropriate animal model system to test all the compounds for their selectivity towards estrogen receptors and then whether they have higher selectivity than does genistein for estrogen receptor beta compared to estrogen receptor alpha. Then the compounds need to be tested for their usefulness in a method of reducing the vascular hyperreactivity in smooth muscle cells and in a patient (claims 9-16) comprising administering to the patient an effective amount of the drug. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Furthermore, one of ordinary skill in the art would have to test the above said compounds in concert with hormone replacement therapy. The specification enables the treatment of vasospasm with estriol and shows comparison of estrogen receptor activities of estriol, 3βAdiol, DPN, genistein and epiestriol. Claim 1 compass a huge number of selective estrogen receptor beta agonists other than the compounds listed in the specification and therefore, it would require undue, unpredictable experimentation to practice the claimed invention of comprising administering every single selective estrogen beta receptor agonist that has higher selectivity than does genistein for estrogen receptor beta compared to estrogen receptor alpha. Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Response to Arguments

Applicants' argue that art cited by the examiner does not support the Examiner does not support the Examiner's contention, but rather supports the contention of Applicant that it is not the particular chemical compound that is important, but what is important is that it is an agonist of the ER-beta receptor. Because the ER-beta receptor, when activated, produces certain results, any agonist of ER-beta will produce these results. In response, prior art has been cited in the enablement rejection to show what is known in the literature. The reference Harris et al. (Endocrinology, 144, 10, 4241-49) teach an ER-beta selective ligand, ERB-041. The authors state that they expected the compound would be useful in hormone therapy as ER-beta is an attractive drug target for hormone therapy. However, the authors found that the ER-beta selective ligand, ERB-041 is inactive in a large panel of estrogen responsive models and does not prevent bone loss or weight gain after overiectomy (p 4246, col. 2, last para). This clearly shows that how all ER-beta agonists can be different and need not possess the expected properties of an ER-beta agonist compound. The claims of the instant application are broad with respect to all selective estrogen receptor beta agonist compounds that have a higher relative selectivity than does genistein for ER-beta compared to ER-alpha. There is a lot of undue experimentation involved in first checking the ER-beta activities of beta agonist compounds and then comparing their relative activity against genistein. As stated above there are quite a number of ER-beta ligands available and this does not include the ones yet to be discovered. After establishing the activity one of ordinary skill in the art would have to test the compounds

whether they reduce the vascular hyperreactivity. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of comprising administering every single selective estrogen beta receptor agonist that has higher selectivity than does genistein for estrogen receptor beta compared to estrogen receptor alpha in a method of reducing vascular hyperreactivity.

Applicants' argue that the specification provides examples with ER-beta agonists and their activity and also examples show the effectiveness of epiestriol, DPN, 3βAdiol and estriol in vasospasms in vitro and estriol protection in vivo models and hence have provided sufficient data to establish that estrogen beta receptor agonists that are selective for ER-beta over ER-alpha in a method of reducing vascular reactivity. In response, Applicants, have provided in vivo data for estriol for treating vasospasms and have provided comparison data for effects of estriol with 3βAdiol and epiestriol in vitro on Ca2+ responses in rhesus coronary VMC (example 9) and comparison data for estrogen beta receptor agonists (genistein, DPN) in measurement of estrogen receptor beta activity. However, the claims are broad with respect to all selective estrogen receptor beta agonist compounds that have a higher relative selectivity than does genistein for ER-beta compared to ER-alpha. There is a lot of undue experimentation involved in first checking the ER-beta activities of beta agonist compounds and then comparing their relative activity against genistein. As stated above there are quite a number of ER-beta ligands available and this does not include the ones yet to be discovered. After establishing the activity one of ordinary skill in the art would have to test the compounds whether they reduce the vascular hyperreactivity. Furthermore, the

compounds need to be tested in vitro and in animal models whether the compounds work in concert with a hormone replacement therapy before administering the ER-beta agonist to a patient as there may be drug interactions involved in a combination therapy. Side effects of estriol are known in the art (http://www.patientsville.com/medication /estriol _side_effects.htm,Estriol Side Effects Report #5318690-8). The specification teaches only the administration of estriol to rhesus monkeys to show the effect of estriol in vasospasm. However, there are no models or working examples in the specification to indicate that the drugs claimed in claim 1 will work in concert with hormone replacement therapy. Estrogen (http://www.medicinenet.com/estrogens-oral/article.htm#) document highlights the side effects and warns the patients of the potential risks of taking estrogens. Obviously, one of ordinary skill in the art would not only take note of such effects but to take precautions of adding another drug such as ER-beta agonist in the hormone replacement therapy (HRT). It would be an undue experimentation to a person of ordinary skill in the art to select a ER-beta agonist compound from the broadly claimed compounds and test in vitro and then in animal models and administer to a patient in reducing vascular reactivity and further use the same drug in concert for HRT after a series of experiments for HRT therapy. Accordingly, the claims as such are not enabled.

Allowable Subject Matter

Claims 4-10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed.

The rejection from the previous office action has been maintained. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
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